## REMARKS

Claims 1, 4-5, 7 and 15-24 are pending in this application.

**Rejections Under 35 USC 112, First Paragraph**

Claims 1, 4, 5, and 7 have been rejected under 35 USC 112, first paragraph as allegedly lacking an enabling disclosure. Without acquiescing to the rejection, and solely in order to promote the progress of this application, the claims have been amended. In particular, the term "variant" has been replaced with the expression "fragment comprising a functional integrin binding site of lactadherin." Such fragments are clearly defined in the application. In particular, the sequence of lactadherin is provided, the location of the integrin binding site is provided, and various methods of producing fragments are disclosed. Withdrawal of the rejection is thus respectfully requested and Applicants reserve the option in the future to present evidence as to the scope and enablement of the use of functional "variants" of the compounds in the methods as claimed.

**Prior Art Rejections**

The claims are not anticipated by USP 5,505,955 or WO 95/15171 because the references do not disclose an element of the claimed invention and thus cannot be rendered invalid under § 102.

**USP 5,505,955**

USP 5,505,955 essentially relates to non-immunologic methods of treating diarrhea. The proposed method is based on the property of a biological material or complex to bind specifically to rotaviruses, thereby inhibiting rotavirus infection. More particularly, the patent proposes to use an agent selected from:

- defatted human milk fat globule,
- the human milk macromolecular fraction,
- the human milk mucin-70 Kd apparent MW glycoprotein-46 Kd apparent MW HMFG glycoprotein complex,
- the 46 Kd apparent MW HMFG glycoprotein,
- a polypeptide comprising an amino acid sequence having the rotavirus-binding specificity of the 46 Kd apparent MW HMFG glycoprotein, and
- mixtures thereof.

As indicated column 4, lines 59-67 of USP 5,505,955:

> *"One advantage afforded by the non-immunological milk agent of the invention over prior art products relies on the fact that the present agents bind to many strains of human rotaviruses as well as to rotaviruses of other species, e.g., mouse and simian, inhibiting viral replication of all strains tested, and prevent rotavirus-associated diarrhea in vivo. Thus, the agent of this invention provides protection for the treatment of e.g., diarrhea caused by a wide range of rotavirus strains."* (emphasis added)

This is in clear contrast with the claimed invention, which relates to the stimulation of an immune response against antigens, not to the inhibition of virus infection. To clarify the nature of the invention, the term "stimulating" is used in claim 1, as amended, to avoid any confusion with non-immunologic methods. The invention furthermore stems from the unexpected ability of lactadherin to interact with dendritic cells and to deliver antigens to said cells, while the '955 patent relates to the interaction between a complex biological product and a virus. Finally, the '955 patent is directed at treating diarrheal condition in a subject, which is clearly remote from the stimulation of an immune response, for instance, for cancer treatment. Thus, the '955 patent does not disclose a claimed element of the present invention and cannot anticipate under § 102(d) due to the absence of a disclosure of an element of the pending claims.

Furthermore, the Peterson et al. '955 patent expressly distinguishes so-called immunologically-based methods from those methods described in the '955 patent.

Column 4, lines 29-36 of the '955 specification state:

> *The method of the invention provides significant advantages over the prior art methods for the treatment of diarrhea. The prior art has focused on immunologic methods in the search for a therapy against diarrhea caused by infectious agents. Immunologically-based methods, however, are ineffective for treating immuno-deficient individuals who cannot muster the needed immunological reserve to fight the pressure of the virus. ...*

Moreover, Column 7, lines 27-32 of the '955 specification state:

> *The agent of this invention exhibits additional advantage for the treatment of infants and children since, as already indicated, its components are normal constituents of human milk in the human diet. The present agent is thus unlikely to elicit toxic, immunological or allergic reactions in treated subjects.*

Clearly, the modes of action, the pathways and the biological effects contemplated and disclosed are distinct and not correlated and this document fails to disclose or teach a method of stimulating an immune response in a subject using lactadherin.

Because the '955 patent aims at inhibiting rotavirus infection by direct interaction with the virus, the stimulation of immune cells such as dendritic cells is clearly not inherently disclosed or expressly taught by this document.

The Examiner's citation and quotation of Application of Best, 562 F.2d 1252, 1255 (CCPA 1977) is inapposite. The quoted language from Best is the CCPA's affirmance of the rejection of product claims on the basis that the prior art reference disclosed similar compositions. The actual method claims at issue in Best were only rejected because the court found that "all process limitations of [the] claim [ ] are expressly disclosed ..." and that the missing element was disclosed through inherency. Here, the process limitations of the method

claims are not expressly disclosed and the element of "stimulating an immune response" is not inherent and is, as indicated by the above excerpts from the '955 patent specification, expressly disavowed by the reference. Therefore, the Best case compels allowance, not rejection, of the pending claims.

Withdrawal of the rejection is respectfully requested.

**WO 95/15171**

WO 95/15171 relates essentially to the same disclosure as USP 5,505,955. Again, the description indicates that the HMFG polypeptide may be used to treat rotavirus infection through direct interaction with said viruses. As stated page 15, lines 7-16:

> *"The polypeptide of the invention also has anti-viral properties. Upon fractionation of the human milk fat globules, human milk globule membrane, which is the globule's macromolecular component, and its acidic protein fraction retain the anti-viral activity. When the defatted milk fat globule fraction is separated into different fractions, the anti-viral activity of human milk remains mostly with the mucin complex. However, when the mucin complex is separated into its components, the highest anti-viral activity is found with 46 Kdalton app. MW HMFG antigen. The 46 Kdalton app. MW HMFG antigen preferentially binds, e.g. simian and human rotaviruses when compared to the 70 Kdalton app. MW HMFG antigen and the 46 Kdalton MW HMFG antigen depleted milk mucin."* (emphasis added)

This paragraph clearly indicates that the activity lies in a direct interaction with a rotavirus, and that this activity is mostly expressed with a complex biological material (mucin complex) rather than an isolated 46Kd HMFG molecule. Furthermore, as indicated on page 17, lines 33-34: *"The present agent is thus unlikely to elicit toxic, immunological or allergic reactions in treated subjects"* (emphasis added). Clearly, the disclosure in the reference does not contemplate or teach the stimulation of an immune response, particularly the stimulation of dendritic cells, as presently claimed and the reference cannot anticipate under § 102 because of the absence of the disclosure of an element of the pending claims.

The present invention shows, for the first time, that lactadherin has advantageous

properties such as the ability to stimulate dendritic cells, and to deliver antigens to dendritic cells. By stimulating such activity, it is now possible to produce effective CTL responses in patients in order to treat or prevent various diseases.

It is thus believed that the invention is novel and inventive over the prior art and that the claims are in condition for allowance.

Respectfully submitted,

**LYON & LYON LLP**

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By: _____
Kurt T. Mulville, Reg. No. 37,194

633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
(949) 567-2300 X 1124 Telephone
(213) 955-0440 Facsimile

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

IN THE CLAIMS:

Please amend claims 1, 4, 5 and 7 as follows:

1. (Amended) A method of [regulating] stimulating an immune response in a mammal, the method comprising administering to said [the] mammal a lactadherin or a fragment [variant] thereof, said fragment comprising a functional integrin binding site of lactadherin.

4. (Amended) The method of claim 1, wherein phagocytosis of antigens by dendritic cells is stimulated in said [the] mammal.

5. (Amended) The method of claim 1, wherein cross-priming of antigens is stimulated in said [the] mammal.

7. (Amended) The method of any one of claims 1-5, wherein said [the] lactadherin or fragment [variant] thereof is human lactadherin or a fragment [variant] thereof.